REMARKS

Claim amendments

Claim 24 is amended to incorporate the additional limitation that the depletion caused by a reference infusion persists for at least two weeks after the infusion. This limitation, as well as the reference dosage of 10 mg/m^2, is supported, e.g., by the example described under heading III.B.i. at pages 56-57. The "wherein" clause is restructured to emphasize that it refers to a measurement of biological activity in a reference system, and does not constitute or refer to a step required as part of the claimed method. The claim is expressly limited to the treatment of human patients, as supported by the disclosure generally.

The amendments are necessary and were not earlier presented because they address rejections first set forth in the final Office action. The amendments do not add new matter to the disclosure. Accordingly, applicant requests that the examiner enter the amendment.

Administrative matter

Applicant acknowledges the objection to the declaration and reiterates that it will provide a substitute declaration.

Rejections under 35 U.S.C. § 112, first paragraph

The Office rejects the claims on various grounds under the written description requirement of § 112, first paragraph. Applicant respectfully traverses these rejections.

Recitation of only the heavy or light chain in claims 31 and 32

The Office's position is that because the working examples involve only antibodies in which both the heavy and light chains appear of C2B8 appear in a single antibody, the disclosure does not support the recitation of the exemplified chains singly.

The disclosure, taken as a whole, does not fairly teach that the two chains of C2B8 must always be employed in the same antibody. The specification teaches that the TCAE-8 vector was constructed for the purpose of facilitating the coexpression of *different* heavy and light chain variable domain inserts, thus to enable the rapid production and evaluation of a variety of antibodies. It also teaches that the component Ig chains may be separately expressed or co-

expressed using separate vectors. Thus, the specification describes a system deliberately designed to provide flexibility that, in the Office's view, the disclosure does not support. Applicant submits that this deliberate design is in fact evidence that the heavy and light chains of C2B8 are not disclosed to be an obligatory pairing.

The claims are also properly supported inasmuch as they properly depend from and further limit claim 24. The independent claim requires a complete and functional chimeric antibody. Dependent claims 31 and 32 simply recite limitations with respect to individual components of the antibody. There is no requirement in the law that a claim that depends from a properly supported independent claim recite further limitations as to every element or component required by the base claim.

90% depletion for antibodies other than C2B8

The Office considers that the "90%" limitation is supported only for the exemplary C2B8 antibody. Applicant does not agree. The specification clearly teaches that C2B8 is but one antibody that is representative of the genus of chimeric antibodies to which it belongs, and that the invention is not limited to that particular embodiment. There is no objective teaching in the disclosure, and no evidentiary basis for the Office's inference, that the properties of C2B8 are or are expected to be singular. The preponderance of the evidence of record weighs in favor of a finding that other antibodies of the invention, and not only C2B8, would have the recited properties.

90% depletion in subjects other than monkeys

The Office takes the position that because 90% depletion is exemplified only in a monkey model, the disclosure does not support the recitation of such depletion in a human. This perspective directly conflicts with objects of the invention stated at the first full paragraph on page 8 of the specification: "the treatment of B cell lymphomas in primates, including, but not limited to, humans."

As those skilled in the art appreciated, non-human primates are regarded as excellent model systems for the treatment of humans. The specification teaches that the chimeric antibodies of the invention cause the depletion of peripheral B cells in treated subjects; 90% is an

exemplary benchmark for such depletion. As the disclosure teaches that the invention involves methods for the treatment of primates generally, *including* humans, the Office has no evidentiary basis for drawing a distinction between the invention as it is embodied in treatments of human and non-human primates.

CDRs – claim 44

Claim 44 is rejected on the grounds that the disclosure does not support "antibodies with human framework regions or murine framework regions other than those found in SEQ ID NO 7 or 11," which as the examiner correctly observes, claim 44 would encompass. None of the claims, however, recite or require "antibodies with human framework regions or murine framework regions other than those found in SEQ ID NO 7 or 11." Applicant notes that several of the claims, including independent claim 24, would encompass such antibodies. But, like claim 44, claim 28 is properly supported with respect to the limitations it affirmatively recites. Claim 44 is properly supported by the disclosure, among other reasons, because the exemplified chimeric C2B8 embodies its limitations. The Office's objection is directed to a claim that is not presented for examination.

Rejection under 35 U.S.C. § 103(a)

Claims 24, 33, and 34 are rejected under § 103(a) over Press (*Blood*, 1987) in view of Hellstrom (WO 92/07466) and Robinson ('362 or WO 88/04936), and claims 41 and 42 are rejected further in view of Eary (*J. Nuc. Med.*, 1990). Applicant traverses the rejections as to the amended claims and requests reconsideration.

The essence of the rejection as stated in the final Office action is that Press teaches a therapeutic method using a murine monoclonal antibody that results in the functional response recited in claim 24, and the Office concludes that it would have been obvious to substitute a chimeric anti-CD20 antibody for the murine antibody used in the method of Press.

Claim 24 has been amended to require functional properties that are not characteristic of the method described by Press. The amended claim requires that the depletion that results from a single administration of 10 mg/m^2 of antibody be maintained for at least two weeks. As is evident from Fig. 2 of Press, administration of murine antibody 1F5 results in only transient

depletion of B cells; the cell population substantially recovers in less than a two-week timeframe. Thus, the claimed method now requires antibodies having functional capabilities that the prior art murine antibody does not.

The functional characteristics recited in the amended claim, moreover, would not be expected in view of the cited prior art, taken alone or in combination. Although there is evidence of record to support the view that those skilled in the art had speculated about potential advantages of using chimeric antibodies as human therapeutics, no evidence of record fairly suggests that any chimeric antibody would provide the sustained B cell depletion demonstrated in applicant's disclosure. The evidence of unexpected results is accordingly strong evidence of nonobviousness.

Because the prior art does not teach or suggest methods using antibodies having the recited functional properties, the invention of claim 24, and consequently the inventions of each of the dependent claims, are patentable over the cited prior art.

Conclusion

Applicant believes that this reply fully responds to the outstanding Office action. Withdrawal of the outstanding rejections and allowance of the pending claim are respectfully requested.

Should the examiner have any concerns or questions, he is invited to contact the undersigned.

Respectfully submitted,

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